The epidemiology of pancreatic, gallbladder, and other biliary tract cancers

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Overview

Pancreatic cancer is the fifth leading cause of cancer-related death in the United States and will result in an estimated 29,700 deaths in 2002. In comparison, biliary tract cancer is rare, accounting for approximately 3500 deaths per year. The progression of pancreatic and biliary tract cancer often occurs without early symptoms, and diagnosis takes place late in the natural history of the disease. Consequently, both types of cancers have dismal survival rates, and treatment has little to no effect on prolonging the lives of these patients.

The majority of pancreatic cancer arises in the exocrine pancreas. In the United States, incidence rates among men are approximately 1.3 times those among women, and blacks have 1.6 times the rates of whites. Incidence increases exponentially with age after 30 years old, and 80% of all cases are diagnosed between the ages of 60 and 80. Although pancreatic cancer incidence varies widely around the world, comparisons are challenging because of inconsistencies in diagnostic accuracy. However, industrialized nations appear to carry a higher burden of pancreatic cancer than less developed nations.

In the past 2 decades, epidemiologic studies examining pancreatic cancer have been plagued with methodologic issues associated with studying a highly fatal disease, thereby hindering our understanding of the etiology of pancreatic cancer. Nevertheless, studies have consistently shown that tobacco smoking increases the risk of pancreatic cancer. Strong evidence also supports the association between pancreatic cancer and two medical conditions, chronic pancreatitis, and diabetes mellitus. Given that these

conditions are often present numerous years before the cancer diagnosis, they should be considered as etiologically relevant. A series of recent studies indicate that obesity may be an important risk factor for pancreatic cancer. Other potential lifestyle risk factors include dietary factors such as carbohydrate and meat consumption, and physical activity.

Biliary tract cancer can arise in the gallbladder or extrahepatic bile ducts. Gallbladder cancer is the most common of the two types and occurs more frequently in women than men. In contrast, extrahepatic bile duct cancer is seen more frequently in men. Although biliary tract tumors are relatively uncommon in the United States, certain ethnic groups, notably American Indians and Hispanic Americans, have substantially higher rates than the rest of the population. Gallstone disease is the most important risk factor for gallbladder cancer, increasing the risk by at least 3-fold. Because of the rarity of biliary tract tumors, diagnostic difficulties, and high mortality, other risk factors for this cancer are not well established. Among the potential risk factors are obesity, reproductive and hormonal factors, cholecystitis, biliary tract infections, and family history.

Given the important epidemiologic dissimilarities of pancreaticobiliary cancers, correct classification is critical to improve the quality of epidemiologic studies. A better understanding of the underlying causes of these deadly cancers will provide new leads for early detection, treatment, and prevention.

Pancreatic cancer

Because the majority of pancreatic cancers occur in the exocrine pancreas, and tumors other than adenocarcinomas tumors are quite rare, this article will only focus on exocrine adenocarcinoma of the pancreas.

In 2002, approximately 29,700 men and women in the United States are expected to die of pancreatic cancer, making pancreatic cancer the fifth leading cause of cancer-related deaths.[1] Survival rates are about 4% for the first 5 years after diagnosis, resulting in mortality rates that are almost identical to incidence rates.[2] Although survival rates are highest (16%) when the tumor is localized at diagnosis, less than 10% of tumors are detected at that time.[2] Survival rates have only improved slightly over the past decade because of the lack of significant medical advancements in the early detection of pancreatic cancer.

Pancreatic cancer is very rare in the first 3 decades of life. After age 30, however, incidence rates increase exponentially,[2] peaking in the seventh to eighth decades. Age-adjusted incidence rates in the United States are slightly higher in men than women (10.2 per 100,000 in men vs. 7.8 per 100,000 person-years in women between 1994-98), and are higher in blacks than whites (13.6 per 100,000 in blacks vs. 8.6 per 100,000 person-years in whites).[2] Over the past 2 decades, incidence rates in the United States have decreased by 0.4% per year, with the exception of a small increase of 0.2% per year among black women. [2] Mortality rates have followed a similar pattern over the past 2 decades.[2]

Among white males and females, the highest mortality rates in the United States are observed in the Northeast and around the Mississippi River.[3] Although white females also have elevated rates of pancreatic cancer along the Western coast, white males have low rates in that region.[3] Large variations in incidence and mortality rates are also apparent in different countries and ethnic groups.[4] The highest incidence rates are found in North America (among blacks), northern Europe, and among the Polynesians of Hawaii and New Zealand Maoris.[4] The lowest rates are observed in Africa, South America, and the Indian subcontinent. [4] In some regions, such as Japan, rates have been increasing rapidly in the past 3 decades, suggesting that environmental factors play a particularly important role.

The most common symptoms of pancreatic cancer (weight loss, pain, and jaundice) occur when the tumor is large and often already metastasized to other organs. Consequently, pancreatic cancer patients are diagnosed late in the progression of the disease and, on average, only have a few months to live. In older individuals, the presence of a pancreatic tumor may not be known until an autopsy is performed on the deceased patient. The absence of symptoms in the early stages of pancreatic cancer have limited our understanding of the induction period for this disease (the time between initiation and detection of the tumor).

There are few well-established risk factors for pancreatic cancer. Among the most convincing are cigarette smoking, inherited susceptibility to pancreatic cancer, chronic pancreatitis, and type II diabetes. Other risk factors of pancreatic cancer, including obesity, physical inactivity, gallbladder disease, dietary factors, and occupational exposures are not firmly established because of sparse or inconsistent data.

Tobacco smoking

Several reviews have summarized the literature on cigarette smoking and pancreatic cancer.[5] [6] Most epidemiologic studies report strong associations between cigarette smoking and pancreatic cancer, with relative risks generally ranging between 1.5 and 3.0 for current smokers versus people who have never smoked.[6] Excess risk among past smokers disappears 10 years after smoking cessation.[7] [10] In two combined cohort studies and a large case-control study, dose-response relationships were much stronger when smoking consumption was calculated for the last 15 years (compared with lifetime smoking).[7] [8]

Family history

A number of inherited cancer syndromes increase the risk of pancreatic cancer. These include BRCA2 carriers,[11] [12] familial atypical multiple mole melanoma syndrome (FAMMM),[13] hereditary pancreatitis,[14] hereditary nonpolyposis colorectal carcinoma (HNPCC),[15] and Peutz-Jeghers syndrome.[16] [17] In addition to these hereditary syndromes, an increasing number of studies have reported a familial pancreatic syndrome that cannot be explained by shared environmental factors. [18] [23] The risk of pancreatic cancer is increased by 3- to 5-fold among first-degree relatives of pancreatic cancer cases.[18] [21] [23] In a prospective study of familial pancreatic cancer kindreds, the incidence of pancreatic cancer among first-degree relatives was 18-fold higher than expected (according to population-based data from the Surveillance, Epidemiology, and End Results program [SEER]). [22] A recent study found that the risk of pancreatic cancer may be even higher (8-fold) among first-degree relatives who smoke cigarettes.[23] Smoking may also affect the risk of pancreatic cancer among individuals with hereditary pancreatitis; one study demonstrated that age of onset was approximately 2 decades earlier among smokers with this inherited susceptibility.[24]

Chronic pancreatitis

Individuals with this medical condition have been reported to have risks up to 16 times higher than healthy individuals.[25] Given that this condition is relatively rare in the general population, only a small percent (3%-4%) of pancreatic cancers may be attributed to this condition.[25] Acute pancreatitis does not appear to be related to the risk of pancreatic cancer; therefore, prolonged inflammation observed in chronic pancreatitis patients is hypothesized to initiate, or at least aid the progression of a pancreatic tumor.[25]

Diabetes mellitus

There has been a long-standing debate about whether diabetes mellitus is a risk factor for, or

consequence of, pancreatic cancer. Earlier case-control studies could not adequately address this question because the presence of type II diabetes in cancer patients was not assessed before disease onset. However, a recent meta-analysis included 20 studies that assessed duration of diabetes before pancreatic cancer. [26] The findings suggest that those individuals with diabetic histories of 5 or more years have a 2-fold elevation in pancreatic cancer risk compared with those without a history of diabetes, or diabetes of less than 5 years duration (95% CI [1.2, 3.2]).[26] Several recent studies, including 3 large cohorts that assessed diabetes history before pancreatic cancer diagnosis, found elevated relative risks of pancreatic cancer (ranging from 1.3 to 1.7) for individuals with long-standing diabetes (10 or more years).[27] [30] If a diabetic state was simply a consequence of a pancreatic tumor, it is unlikely that any association would be observed between long-standing diabetes and risk of pancreatic cancer.

Obesity

In several recent prospective studies, and two case-control studies in which only direct interviews were used, elevated risks of pancreatic cancer were observed among overweight and obese men and women. [31] [34] In another cohort study, the association was apparent among men, but not among women.[35] Statistically significant relative risks for these associations ranged from 1.2 to 3.0, and dose-dependent relationships were consistently observed. One cohort study did not report an association between Body Mass Index (BMI, kg/m^2) and pancreatic cancer risk. However, this study population consisted of elderly people, most of whom were not overweight (the cutoff points for the top BMI categories were less than 24 in both men and women). Therefore, the absence of a clearly defined overweight category might explain the lack of association.

There are several reasons why a number of other studies examining weight or BMI in relation to pancreatic cancer reported no association. Because weight loss often occurs several years before pancreatic cancer diagnosis and is often a primary factor leading to the detection of this cancer, studies measuring weight after disease diagnosis may have resulted in biased weight recall. Alternatively, biases may have occurred when weight was not obtained for deceased cases, or when it was obtained through indirect interviews. In prospective studies, where weight is obtained before disease diagnosis and individuals are followed over time for numerous years, these types of biases cannot occur.

The association between type II diabetes and pancreatic cancer risk may be the result of years of elevated postload glucose concentrations and gradual impaired glucose tolerance. In a recent prospective study of people who are not diabetic, postload glucose concentration was directly associated with pancreatic cancer risk in men and women.[35] This study supports the hypothesis that impaired glucose tolerance and diabetes play a role in the carcinogenesis of pancreatic cancer. Obesity has been linked to significant metabolic abnormalities, including insulin resistance and diabetes and, consequently, may be related to the risk of pancreatic cancer.

Physical activity

To date, few studies have examined physical activity in relation to pancreatic cancer risk. However, because exercise is known to improve glucose tolerance, even in the absence of weight loss, this factor could be an important modifiable risk factor for pancreatic cancer. In a recent publication of two prospective studies, regular moderate exercise was associated with decreased risk of pancreatic cancer in both men and women.[31] The association was strongest among individuals who were overweight (especially among those considered obese [BMI >30 kg/m^2]), and was not apparent among those who were not overweight. Because lean individuals are less likely to have metabolic abnormalities, they may not benefit from exercise in the same way as overweight individuals. These findings agree with the hypothesis that impaired glucose tolerance and insulin resistance play a role in the carcinogenesis of pancreatic cancer. Another recent study observed a similar association between exercise and the risk of

pancreatic cancer, although the association was stronger in men than women.[34]

Dietary factors

Although data on diet and pancreatic cancer are not limited, findings have been inconsistent. Problems with these studies include use of proxies to obtain dietary information (on cases), recall bias, low response rates among cases because of high fatality rates, and poor dietary assessment tools.

Inverse associations between fruit and vegetable intake and pancreatic cancer risk have been consistently observed in epidemiologic studies in the past 3 decades. Considering all food groups, a panel of experts judged fruits and vegetables most likely to be associated with pancreatic cancer.[36] However, a number of prospective studies have observed no associations with fruit and vegetable intake, [36] [37] suggesting that the findings from case-control studies, which comprise the majority of studies, may have been biased by differential recall of dietary intake. This does not exclude the possibility that certain constituents of fruits and vegetables, such as vitamin C or folic acid,[38] [39] may be related to the risk of pancreatic cancer. More studies are needed to clarify these issues.

Other dietary items which have been consistently related to pancreatic cancer risk include the intake of carbohydrate, refined sugar, cholesterol, and meat (reviewed in detail).[36] [40] Compounds derived from cooking meats at high temperatures (e.g., heterocyclic amines), or from certain preserving methods (e.g., cured and smoked), may explain some of the excess risk. However, epidemiologic studies to date have been limited by difficulties in assessing the level of these compounds in consumed foods.

The largest literature on dietary intake and pancreatic cancer focuses on coffee and alcohol consumption. The totality of the evidence from several decades of epidemiologic studies does not support a relation between coffee or alcohol intake and the risk of pancreatic cancer (reviewed in detail in two International Agency for Research on Cancer [IARC] monographs).[41] [42] However, there remains the possibility that excessive alcohol consumption is associated with the risk of pancreatic cancer.[27]

Cholecystectomy and cholelithiasis

Both gallbladder disease and removal of the gallbladder have been associated with elevated risk of pancreatic cancer in numerous case-control studies (previously reviewed).[43] However, because patients with occult tumors may have a cholecystectomy for presumed symptomatic gallstones months or years before the cancer is diagnosed, it has often been questioned whether these medical conditions are causal factors. In a recent case-control study, a 70% increase in risk remained even after allowing 20 or more years between cholecystectomy and tumor diagnosis.[21] Two large cohort studies (with more than 300 cases each), however, did not observe elevated risks for individuals with cholecystectomy performed at least 2 years before diagnosis [44] [45] or after controlling for obesity and other confounding factors.[45] Similarly, no association was reported for gallstones detected 2 or more years before tumor diagnosis[45] (gallstone information was not available in the other large cohort[44]).

A previous population-based cohort study reported a 30% elevation in pancreatic cancer risk with gallstones or cholecystectomy performed 5 or more years before tumor diagnosis, but this study did not adjust for obesity or smoking.[46]

Occupation exposures

A large number of studies have focused on potential occupational exposures in relation to the risk of pancreatic cancer (previously reviewed[43]). Overall, few consistent relationships have been observed.

Research on the possible effect of chlorinated hydrocarbon solvents on pancreatic cancer has been extensive; however, little or no elevation in pancreatic cancer risk was observed in a recent meta-analysis of occupational exposures to chlorinated hydrocarbon (CHC) solvents. [47] The authors of this meta-analysis concluded that strong causal associations between CHC compounds and pancreatic cancer are unlikely.

Biliary tract cancer

Biliary tract cancers can occur in the gallbladder, the extrahepatic bile ducts, or the ampulla of Vater. Cancers that originate in the intrahepatic bile ducts are classified with liver cancer. Relatively little is known about the etiologic factors of biliary tract cancers, largely because these types of cancers are very rare and highly fatal. In 2002, it is estimated that 7100 men and women in the United States will be diagnosed with biliary tract cancer.[1] Of the 3 possible sites of origin, the gallbladder is the most common, followed by the extrahepatic bile ducts. Interestingly, these cancers do not appear to share the same characteristics and risk factors and will thus be discussed separately.

Gallbladder cancer

In the United States, the incidence of gallbladder cancer is almost twice as high in women than men (1.3 per 100,000 vs. 0.7 per 100,000 person-years, respectively, between 1994-98).[48] Although this ratio varies by ethnicity, females are almost always at higher risk. In the United States, the highest incidence rates are observed among Hispanics and Native American Indians (2.0 per 100,000 and 1.7 per 100,000 person-years, respectively).[48] For all ethnic groups, and across both sexes, incidence rates increase exponentially with age after 40 years of age.[48]

Survival rates are higher for gallbladder cancer than for pancreatic cancer, although they can still progress rapidly and be fatal.[49] The 5-year survival rates for localized tumors are substantially greater (40% in women; 55% in men) than for regional tumors (6% in women; 1% in men). Because a quarter of the cases are detected at early stages, the overall 5-year survival rate for this tumor is slightly higher than that for pancreatic cancer (17% vs. 4%, respectively). [49] In the United States, mortality rates for gallbladder cancer have dropped over the past 2 decades, particularly among whites (1.2 per 100,000 in 1969-1978 to 0.6 per 100,000 person-years in 1990-1998). [48]

Although little is known about the etiology of gallbladder cancer, there is little doubt that gallstone disease is the main risk factor. The presence of gallstones increases the risk of gallbladder cancer more than 3-fold and appears to be stronger among ethnic groups that have higher rates of gallbladder cancer. [50] Other risk factors for gallbladder cancer include those that may themselves be risk factors of gallstone disease, such as obesity, reproductive and hormonal factors, and certain dietary factors.[49] Other factors, such as cholecystitis, biliary tract infections, and family history, may also play a role in the etiology of gallbladder cancer.[49]

Other biliary tract cancer

Incidence and mortality rates for "other" biliary cancers, those originating in the extrahepatic ducts or ampulla of Vater, are combined in the SEER database because of their low rates. In contrast to the trends observed with gallbladder cancer, incidence rates for these types of tumors are more common in men than women, especially among whites (1.4 per 100,000 in white males vs. 0.9 per 100,000 person-years in white females, between 1992-1998).[48] Native American Indians and Asians have elevated incidence rates compared with whites or blacks.[48] Extrahepatic bile duct cancers are especially high in Miyagi and other cities in Japan and among Japanese in Hawaii and Los Angeles.[49] Overall 5-year survival rates for

these tumors are similar to those for gallbladder tumors. [49] Mortality rates in the Unites States have declined over the past 2 decades and currently range from 0.4 per 100,000 person-years among white or black women to 0.7 per 100,000 person-years for Asian or American Indian men.[48]

To date, epidemiologic data for biliary tract tumors other than gallbladder is extremely sparse. Subsequently, risk factors of these tumors are poorly understood. Gallstone disease and smoking history were associated with elevated risk of extrahepatic bile duct cancers in a case-control study in Los Angeles.[51] In the same study, obesity increased risk of extrahepatic bile duct cancer, but not cancer of the ampulla of Vater.[51] History of cholecystectomy has been associated with elevated risk of ampulla of Vater cancer[46] [52] and decreased risk of extrahepatic bile duct cancer.[46] [53] Primary sclerosing cholangitis is also a well recognized risk factor for bile duct cancer.

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